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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,878	01/23/2002	Macino Giuseppe	6360	5622

7590 05/05/2004

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/913,878	GIUSEPPE ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *12,13 and 15-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,14 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *8/20/01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/20/01,2/20/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Sequence - Notice to Comply

DETAILED ACTION

Claims 1-23 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I in response filed on 3/15/04 is acknowledged. The traversal is on the ground(s) that the invention of Group VIII can be examined together with the invention of Group I. This is found persuasive and the inventions of Groups I and VIII are rejoined.

Accordingly, claims 12, 13, 15-22 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1-11, 14 and 23 are currently under examination.

The restriction requirement of Groups I-VII is therefore made FINAL.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

The information disclosure statement filed on 8/20/01 and 2/20/02 has been considered. A signed and initialed copy of the IDS is transmitted with this Office Action.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Sequences are disclosed in the specification and/or figures that are not identified by their sequence identifier (i.e., SEQ ID NO:). For example, in Figure 5, several amino acid sequences are disclosed, but none are identified by their sequence identifier. The Brief Description of the Drawings at page 12 also does not identify the sequences by SEQ ID NO. **Applicant is reminded that the entire specification and figures should be reviewed for sequence disclosures** and that each sequence disclosed in the specification must be identified by its sequence identifier (i.e., SEQ ID NO:). The specification must be amended to identify all disclosed sequences by their sequence identifier (i.e., SEQ ID NO), in accordance with 37 CFR 1.821(d).

Specification

The disclosure is objected to because of the following informalities: The specification lacks section heading. In addition, applicant is advised to change "not human animal" to "non-human animal" on page 10, lines 14-15.

Appropriate correction is required.

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.

(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(e) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) BRIEF SUMMARY OF THE INVENTION.
(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(h) DETAILED DESCRIPTION OF THE INVENTION.
(i) CLAIM OR CLAIMS (commencing on a separate sheet).
(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-11, 14 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is set forth by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . .[emphasis

added]." The written description requirement has been well established and characterized in the case law. A specification must convey to one of skill in the art that "as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. The claims are drawn to nucleotide sequences encoding proteins that have a silencing activity and comprise a RNA-dependent polymerase domain that has 30%, 40%, 50% or 100% homology to the amino acid sequence from 710 to 1282 of SEQ ID NO:1, expression vectors comprising said nucleotide sequence, prokaryotic organisms and fungus transformed with said vectors, and use of the nucleotide sequence molecules to modulate gene silencing in plants, animals and fungi. The claimed nucleic acid encompasses potentially a large genus of nucleotide sequences that shares homology with a portion of SEQ ID NO:1. In addition, claim 5 recites a functional portion of a protein that has amino acid sequence of SEQ ID NO:1, which also encompasses a large number of nucleic acid different size and structure. The specification only discloses one protein having amino acid sequence of SEQ ID NO:2 (not SEQ ID NO:1, which is a nucleic acid sequence instead) which is

involved in post transcriptional gene silencing (quelling) in *Neurospora Crassa* filamentous fungus. The specification discloses that a portion of this protein (aa.710-aa.1282) shares a degree of homology with a tomato RNA-dependent RNA polymerase domain. However, the specification fails to disclose what domain(s) of the protein is necessary and sufficient for the silencing activity. The specification only provides teachings with regard to the complete protein and its role in gene silencing. Although the protein has a domain homologous to a tomato RNA-dependent RNA polymerase domain, the specification fails to provide a correlation between this domain and the gene silencing function. Furthermore, the specification fails to teach other domain(s) and their functional relevance to the observed silencing activity of the protein represented by SEQ ID NO:2. Lastly, the specification fails to disclose whether this protein or parts of this protein has gene silencing activity in other species such as plant and animal cells. As such, it is unclear what is the structural requirement for the protein to have gene silencing activity in *Neurospora Crassa* filamentous fungus or other species. The prior art does not provide sufficient information to discern a structure-function relationship for a nucleic acid encoding a protein having homology to RNA dependent RNA polymerase domain and with gene silencing activity in fungus, plant and animal. The prior art thus cannot be used to overcome the deficiencies of the instant specification. As such, the structural functional relationship is missing. Therefore, the specification fails to describe a representative number of species of the claimed genus by their complete structure or other identifying characteristics, and the written description requirement is not satisfied.

Claims 1-5, 7-11, 14 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The nature of the invention:

The claims are drawn to nucleotide sequences encoding proteins that have a silencing activity and comprise a RNA-dependent polymerase domain that has 30%, 40%, 50% or 100% homology to the amino acid sequence from 710 to 1282 of SEQ ID NO:1, expression vectors comprising said nucleotide sequence, prokaryotic organisms and fungus transformed with said vectors, and use of the nucleotide sequence to modulate gene silencing in plants, animals and fungi.

The breadth of the claims:

The breadth of claims is broad. The broadest claim (1) encompasses a nucleotide sequence encoding for a protein characterized in having a silencing activity and comprises a RNA-dependent RNA polymerase domain that is 30% homologous with the amino acid sequence from 710 to 1282 of SEQ ID NO:1. Homology of 30%, 40%, 50% or even 100% to a

portion of SEQ ID NO:1 provides a great number of polynucleotides, most of which may be incapable of affecting gene silencing/quelling. Claim 11 is drawn to a prokaryotic organism transformed by using an expression vector active in bacteria which comprises a bacterial promoter. However, a prokaryotic organism is not limited to bacteria. The bacterial promoter will not function in all prokaryotic organism. Thus, the breadth of claim is broad.

The teaching of the specification:

The teaching of the specification is limited. The specification only teaches a qde-1 gene isolated from *Neurospora Crassa* filamentous fungus is involved in post transcriptional gene silencing in *Neurospora Crassa* filamentous fungus. The specification teaches that sequence analysis of the qde-1 gene detected a region having a significant homology with a RNA-dependent RNA polymerase isolated from tomato. However, the specification does not teach or provide working examples concerning the degree of homology to the 710-1282 domain and its functionality. Furthermore, there are no teachings with regard to whether 710-1282 domain is necessary or sufficient for the silencing activity. Moreover, the specification fails to teach whether the protein encoded by qde-1 has the claimed silencing activity in species other than *Neurospora Crassa* filamentous fungus. As such, one skilled in the art would have to rely on the teaching of the prior art to use the claimed invention.

The state of art and the level of predictability in the art:

The state of art is silent with regard to the use of the 710-1282 domain to control post transcriptional silencing in an organism. Furthermore, the prior art does not indicate the role or the importance of this domain during silencing. The art is also silent on the use of polynucleotides encoding proteins comprising 30%, 40%, 50% homologous to 710-1282

domain, etc., for the purpose of silencing. Moreover, predicting function based on sequence homology is an inherently unpredictable art. As a result, the ordinary skilled artisan could not turn to prior art to determine the usefulness of certain proteins having a particular degree of homology to the indicated domain. The level of skill in the art is highly undeveloped. A search of the prior art reveals that the applicants are the first to identify this activity in a protein having homology to an RNA-dependent polymerase domain. However, as discussed above, the specification does not provide sufficient guidance to indicate what portions and what degree of homology to the RNA-dependent polymerase domain are necessary and sufficient to elicit silencing. Applicant is attempting to predict function based on homology, with little evidence to support the conclusion of function. Such practice is highly unpredictable as evidenced by Everett et al. (Nature Genetics 17: 411-421, 1997) in view of findings of Scott et al. (Nature Genetics 21: 440-443, 1999). In summary, Everett predicted the function of a particular protein, "Pendrin", as a sulphate transporter protein based on its sequence homology to other sulphate transporter. A subsequent study later revealed that the Pendrin protein was indeed not a sulphate ion transporter, but a transporter of chloride and iodide. Scott then concludes that the results underscore the importance of confirming the function of a protein even when database searches reveal significant homology (see page 441, 1st col., 4th paragraph). Thus predicting function of a protein based on sequence homology is unpredictable.

Amount of experimentation required:

Based on the limited teaching from the specification and prior art, whether a nucleotide sequence encoding a protein having 30%, 40%, 50% and 100% homology with 710-1282 domain would have gene silencing activity in any species is unpredictable. The skilled artisan

would have to determine 1) whether or not 710-1282 domain is required or dispensable for the silencing activity; 2) if so, which portion/residues of said domain is necessary for such function. There is very little expectation that the protein will indeed have silencing activity, based upon reasons set forth above. The experimentation is undue and unpredictable trial and error experimentation is required. Therefore, the claimed invention is not enabled by the instant specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 14 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 1-11, 14 and 23, the recitation of "homologous with the amino acid sequence...of SEQ ID NO:1" renders the claims indefinite because SEQ ID NO:1 disclosed in the specification is a nucleic acid sequence, not an amino acid sequence.

Regarding claims 7-10, the recitation of "a promoter that is expressed in bacteria/plant organs/fungi/animals" renders the claims indefinite because a promoter directs the expression of a gene rather than get expressed itself. The specification does not teach how a promoter is expressed. As such, the metes and bounds of the claims cannot be expressed.

Regarding claims 8-10, the recitation of "expression vector comprising...in a sense and anti-sense" orientation renders the claims indefinite because it is unclear how the nucleotide

sequence can be in both a sense and anti-sense orientation. In addition, it is suggested to add a comma at line 2 after "plant organs" in claim 8 so that the sentence is more clear.

Regarding claim 11, the recitation of "prokaryotic organism transformed by using the expression vector active in bacteria according to claim 7" renders the claim indefinite. Claim 7 recites a promoter expressed in bacteria, however, the prokaryotic organism is not limited to bacteria. As such, it is unclear whether the expression vector is active in said prokaryotic organism.

Regarding claims 11 and 14, the recitation of "Prokaryotic organism/fungus transformed by using the expression vector" renders the claims indefinite because it is unclear whether the prokaryotic organism or fungus is actually transformed with the expression vector. As such, the metes and bounds of the claims cannot be established.

Claim 23 provides for the use of the nucleotide sequence of claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

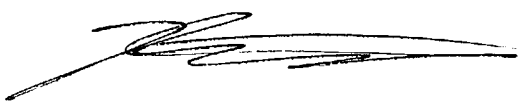
The claims are drawn to a nucleotide sequence encoding for a protein characterized in having a silencing activity and a RNA-dependent RNA polymerase domain, wherein the domain having sequence homology to SEQ ID NO:1, which is a product of nature. Therefore, it is directed to a non-statuary subject matter.

Claim 23 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Celine Qian, Ph.D.